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EXAMINER	
SHAFER, SHULAMITH H	

ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/573,625	PROUDFOOT ET AL.	
	Examiner	Art Unit	
	SHULAMITH H. SHAFER	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-39 and 44* is/are pending in the application.

4a) Of the above claim(s) *27,33,38 and 39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-26, 28-32, 34-37 and 44* is/are rejected.

7)☒ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 March 2006* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/28/06,10/3/07,3/9/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, And/Or Claims:

Applicants' amendment of 18 May 2009 is acknowledged. Claims 40-43 have been canceled. Claim 24 has been amended and the amendment made of record. Claim 44 is newly presented and made of record.

Restriction Requirement:

Applicants' election, without traverse of Group I, claims 24-37, drawn to a method for treating or preventing autoimmune, inflammatory, or infectious diseases comprising administration of a monomeric variant of a homodimer forming chemokine, in the reply filed on 18 May 2009 is acknowledged. In response to requirement for species election, Applicants have elected SEQ ID NO:2 and multiple sclerosis. Because Applicant did not distinctly and specifically point out the supposed errors in the requirement for species election, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 24-39 and 44 are pending in the instant application. Claims 38 and 39 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 27 and 33 are withdrawn from further consideration as being drawn to a non-elected species, SEQ ID NO:4, as the specification identifies the sequence comprising SEQ ID NO: 2 with a further mutation to isoleucine at position 64 of SEQ ID NO: 2 as SEQ ID NO: 4 [paragraph 0013 of PGPUB 20070280958, the PGPUB of the instant application]. Claims 24-26, 28-32, 34-37 and 44 are under consideration to the extent they read on the elected invention.

Priority:

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d) based on an application 03078308.8 filed in European Patent

Office, on 16 Oct 2003. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Information Disclosure Statement:

The Information Disclosure statements (IDS) submitted on 28 March 2006, 3 October 2007 and 9 March 2009 have been considered. The signed copies are attached.

The specification contains a listing of references at pages 46 and 47. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Sequence Rules:

The specification is not in compliance with the requirements of 37 CFR 1.821 through 1.825 of the Sequence Rules and Regulations. Specifically, the application fails to comply with CFR 1.821(d), which states:

> (d) Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequences by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text or claims of the patent application.

Figures 1 and 7B depict sequences. However, these sequences are not identified by sequence identifiers. **Compliance with the sequence rules is required**.

Applicant must submit a response to this Office Action and compliance with the sequence rules within the statutory period set for response to this Office Action.

Objections

Drawings:

The drawings are objected to because Figures 1 and 7B depict sequences without identifying said sequences by SEQ ID NOs: (See discussion above).

Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claims:

Claim 24 is objected to because of the following informalities: the claim contains a typographical/grammatical error. The claim should be amended so that "variant result" in line 4 recites "variant results".

Rejections

35 U.S.C. § 112, Second Paragraph:

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 29 and 35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 29 (a) is drawn to a method "wherein said monomeric variant contains, in the **corresponding** sequence of SEQ ID NO: 2 and SEQ ID NO: 4: a) a Cysteine in position 8, 14, 17, or 77; ....." (Emphasis added by Examiner). Both SEQ ID NOs: 2 and 4 are polypeptides that **consist of 76 amino acids**. Thus, it is unclear what Applicants intend by a Cysteine in position 77. It is unclear if applicants intend a variant that is 77 amino acids long, consisting of a cysteine residue at the C-terminus.

Claim 35 is included in the rejection as dependent upon claim 29.

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 24-26, 28-32, 34-37 and 44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating an autoimmune or inflammatory disease wherein MCP-1 signaling is involved in the disease process, comprising the administration of an effective

amount of a monomeric variant of a homodimer-forming chemokine, wherein said variant is SEQ ID NO:2, or SEQ ID NO:4 or wherein said monomeric variant contains, in the corresponding sequence of SEQ ID NO: 2 and SEQ ID NO: 4: a) a Cysteine in position 8, 14, or 17 or an additional cysteine at the C-terminus of SEQ ID NOs 2 or 4 or b) an alanine or a glycine in position 1 (as recited in Claim 29) or wherein said variant comprises SEQ ID NO:2, or SEQ ID NO:4 or a variant which contains, in the corresponding sequence of SEQ ID NO: 2 and SEQ ID NO: 4: a) a cysteine in position 8, 14, or 17 or an additional cysteine at the C-terminus of said sequences or b) an alanine or a glycine in position 1 and a constant region of a human immunoglobulin heavy chain

does not reasonably provide enablement for

a method of preventing any autoimmune, inflammatory, or infectious disease or

a method of treating any infectious disease or

a method of treating any, unspecified autoimmune or inflammatory disease

comprising administration of any unspecified variant of any homodimer - forming chemokine.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims: Claim 24, the independent claim of the instant invention, is drawn to a method of treating or preventing any autoimmune, inflammatory or

infectious disease comprising administration of any monomeric variant of any homodimer-forming chemokine. Thus, the claim is broadly drawn to administration of any monomeric variant of any chemokine to treat or prevent any autoimmune, inflammatory or infectious disease. Claim 25 recites the limitation wherein the monomeric variant is chosen from: a) SEQ ID NO: 2 b) SEQ ID NO: 4 or c) an active mutant of (a) or (b); or d) a polypeptide comprising (a), (b), or (c), and an amino acid sequence belonging to a protein sequence other than said chemokine.

The scope of the patent protection sought by Applicants as defined by the claims fails to correlate reasonably with the scope of enabling disclosure set forth in the specification and what is known in the art for reasons set forth below.

With respect to prevention

Claims 24-27, 28-37 and 44 require a method of preventing any autoimmune, inflammatory or infectious disease. However, the phrase "preventing autoimmune, inflammatory, or infectious diseases ", given its broadest reasonable interpretation in light of the teachings in the specification, requires that absolutely no individual would present any symptom of any autoimmune, inflammatory, or infectious disease after treatment with an effective amount of a monomeric variants of a homodimer-forming chemokine, or treatment wherein the monomeric variant is SEQ ID NO:2 or an active mutant thereof. There is no evidence, either in the specification or in the prior art, that any method to date can accomplish this goal.

The specification presents the results of the following experiments:

(1) administration of the polypeptide of SEQ ID NO:2 to mice sensitized by ip injection of ovalbumin and challenged with intranasal administration of ovalbumin (a model for allergic lung inflammation) [paragraph 0130].

(2) administration of the polypeptide of SEQ ID NO:2 to mice with EAE (an animal model of multiple sclerosis) [paragraph 0130-0142]

(3) administration of the polypeptide of SEQ ID NO:2 to mice pre-sensitized by application of DNFB to the shaved abdomen and challenged by application of DNFB to the ear (model for delayed contact hypersensitivity) [paragraph 0143].

These data show that administration of the polypeptide of SEQ ID NO:2 reduced the recruitment of cells as assessed in peritoneal lavages in experimental model 1 [paragraph 0145 and Figure 4], improved symptoms in animals with EAE model of MS [paragraph 0146 and Figure 5] and resulted in a decrease in ear swelling in animals with DNFB-induced model of contact hypersensitivity [paragraph 0147 and Figure 6]. However, there is no support for the prevention of any autoimmune, inflammatory or infectious disease, as is required by the claims, and neither can such support be obtained through reasonable extrapolation of the data or teachings in the art.

With respect to treatment of infectious disease

The claims are drawn to a method of treatment of infectious disease comprising administration of the polypeptide of SEQ ID NO: 2 or an active mutant thereof.

The specification teaches that variants of CCL2 (also known as Monocyte Chemoattractant Protein 1 (MCP-1) or Monocyte Chemotactic And Activating Factor (MCAF)) having a single amino acid substitution resulting in an obligate monomer can antagonize the biological activity of natural CCL2 chemokine [paragraph 0011]. The disclosure teaches that such variants may be used in the treatment of autoimmune, inflammatory, or infectious diseases [paragraph 0092]. The working examples are directed to administration of the polypeptide of SEQ ID NO:2 to animals with induced disease that are models of allergic lung inflammation, multiple sclerosis (an autoimmune disease) and delayed contact hypersensitivity (Example 3). These models are models of inflammatory or autoimmune diseases. However, there are no examples, working or prophetic, teaching the utilization of the methods of the instant invention to treat infectious

diseases. There is insufficient guidance on how to utilize polypeptides of the instant invention, which act as antagonists of CCL-2, to treat infectious diseases.

The art teaches (See, for example, Serbina et al. Annu. Rev Immunol. 2008. 26:421-52) inflammatory monocytes respond to microbial stimuli by migrating to sites of microbial infection in response to secretion of the chemokine CCL2 (MCP-1). Such recruitment is essential for defense against bacterial, protozoal and fungal pathogens (abstract). Infections with a diversity of pathogens require CCL2- mediated recruitment of monocytes to sites of infection, where they restrict further microbial growth and invasion (page 441, 2nd column). Thus, one of ordinary skill, aware of the teachings in the art, would be unable to predict that a method comprising administration of an ***antagonist*** of CCL2 (MCP-1) would be effective in the treatment of infectious diseases.

With respect to treatment of any, unspecified autoimmune or inflammatory disease

The claims are drawn to methods of treatment of any autoimmune or inflammatory disease.

The specification teaches CCL2, also known as Monocyte Chemoattractant Protein 1 (MCP-1) or Monocyte Chemotactic And Activating Factor (MCAF), has been identified as having a central role in inflammation, being capable of promoting the recruitment of monocytes and lymphocytes in response to injury and infection signals in various inflammatory diseases, different types of tumors, cardiac allograft, AIDS, and tuberculosis [paragraph 006]. The disclosure envisions that the methods of the instant invention may be used to treat such diverse diseases as, for example: arthritis, rheumatoid arthritis (RA), psoriatic arthritis, osteoarthritis, systemic lupus erythematosus (SLE), systemic sclerosis, scleroderma, polymyositis, glomerulonephritis, fibrosis, fibrosis, allergic or hypersensitivity diseases, dermatitis, asthma, chronic obstructive pulmonary disease (COPD), inflammatory bowel disease (IBD), Crohn's diseases, ulcerative colitis, multiple sclerosis, cancer, septic shock, viral

or HIV infections, transplantation, airways inflammation, graft-versus-host disease (GVHD) and atherosclerosis [paragraph 0092]. As discussed above, the working examples are directed to administration of the polypeptide of SEQ ID NO:2 in animal models of allergic lung inflammation, multiple sclerosis (an autoimmune disease) and delayed contact hypersensitivity.

The art of record (See, for example, Dawson et al. 2003. Expert Opin Ther. Targets 7:35-48) teaches MCP-1 (CCL2) has been implicated in many inflammatory and autoimmune diseases characterized by a monocyte-rich infiltration (page 36, 1st column, 3rd paragraph). However, the reference cautions that "The involvement of MCP-1/CCR-2 in disease is still mainly inferred from studies in animal models, and, in many cases, built upon 'guilt by association'" (page 44, 1st column, 2nd paragraph). Thus, one of ordinary skill in the art would predict that diseases wherein MCP-1 signaling is involved in the disease process, but not any generic inflammatory or autoimmune disease, would be amenable to treatment by the methods of the instant invention.

With respect to administration of any unspecified variant of a homodimer -forming chemokine.

The independent claim of the instant invention, claim 24, is broadly drawn to administration of any monomeric variant of any homodimer-forming chemokine. Claim 25 recites the limitation wherein the monomeric variant is SEQ ID NO:2 or an active mutant of SEQ ID NO:2. Claim 25 can be broadly interpreted as a mutant which has the same biological activity of SEQ ID NO:2 (antagonizing MCP-1 signaling).

Methods comprising administration of any monomeric variant of any homodimer-forming chemokine. or administration of any, unspecified active mutant of SEQ ID NO:2 are not enabled for the following reasons:

The claims envision administration of a monomeric form of any chemokine in the treatment methods of the instant invention. The art recognizes that chemokines comprise a large family of small, chemoattractant proteins which

regulate leukocyte migration in inflammation and immunity. About 50 chemokines have been identified and characterized (Loetscher et al. J Leukocyte Biology 69:881-884, abstract and page 881, 1st column, 1st paragraph). However, applicants have provided guidance and examples of utilization of a variant of only one specific chemokine, CCL2 (also known as Monocyte Chemoattractant Protein 1 (MCP-1) or Monocyte Chemotactic And Activating Factor (MCAF)) in the methods of the instant invention. Applicants have specifically taught administration of the variant of SEQ ID NO:2, which has a single amino acid substitution at position 8 in human CCL2, in the methods of the instant invention (Example 3). Additionally, the specification discloses the following variants of SEQ ID NO:2:

SEQ ID NO:2 with a further mutation to isoleucine at position 64 (SEQ ID NO:4) [paragraph 0012-0013]

SEQ ID NO:2 or SEQ ID NO:4 missing the N-terminal glutamine residue, or comprising alanine or glycine at the N-terminus [paragraph 0150]

SEQ ID NO:2 or SEQ ID NO:4 variants comprising a cysteine in position 8, 14, 17 or added on to the C-terminus (Figure 7A)

A fusion protein comprising SEQ ID NO:2 and an immunoglobulin domain constant region [paragraphs 0052 and 0151].

Insufficient guidance is presented as to how to make and utilize variants of any other chemokine or how to make any other variants of SEQ ID NO:2 such that the required biological activity, that of treating an autoimmune or inflammatory disease is retained. Although the specification provides guidance and examples of mutant CCL2 polypeptides comprising mutations or substitiutions at positions 8, 14, 17 or 64, the language of the claims, reciting "at least one substitution" does not limit the substitutions to only these residues. Claim 24, as written, is directed to a variant of any chemokine comprising any substitutions within the unidentified polypeptide. The specification teaches "The antagonistic properties of the monomeric variants of homodimer-forming chemokines.... can be maintained, or even potentiated, in the active mutants.

This category of molecules includes natural or synthetic analogs ..., wherein one or more amino acid residues have been added, deleted, or substituted [paragraph 0041]. The disclosure additionally teaches "A further group of active mutants of the monomeric variants of the homodimer-forming chemokines ... are peptide mimetics (also called peptidomimetics), in which the nature of peptide or polypeptide has been chemically modified at the level of amino acid side chains, of amino acid chirality, and/or of the peptide backbone. These alterations are intended to provide monomeric variants of the homodimer-forming chemokines having similar or improved properties in terms of preparation, potency and/or pharmacokinetics features" [paragraph 0046]. Thus, the teachings of the specification encompass a myriad of unspecified variants of any chemokine comprising any number of substitutions (or additions or deletions) of naturally occurring or modified amino acids. However, applicants have provided insufficient guidance as to how many amino acids or which specific amino acids may be deleted and which must be retained or which changes to the peptide backbone could be made so that the resulting chemokine monomeric variant would retain with the required, biological activity, that of effectively treating any of the recited diseases.

The art provides some guidance as to structure-activity relationships among the various, identified chemokines. Results from studies of structure activity relationships suggest the importance of the amino-terminal region in binding of the chemokine to its cognate receptor. (Loetscher et al, page 881, 2nd column, 2nd paragraph). However, the reference cautions that "animo-terminal truncation does not yield ...chemokine antagonists necessarily" (page 883, 1st column, 2nd paragraph). Thus, one of ordinary skill would have to undertake undue experimentation to determine which amino acids and how many amino acids may be altered to yield the monomeric peptides retaining the required biological activity.

Protein chemistry is one of the most unpredictable areas of biotechnology. While it is known that many amino acid substitutions are generally possible in

any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequences are critical to the protein's structure/function relationship, as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites; the importance of the amino-terminal region of the chemokine molecule is discussed above. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al, 1990, *Science* 247:1306-1310, especially p.1306, column 2, paragraph 2; Wells, 1990, *Biochemistry* 29:8509-8517; Ngo et al., 1994, *The Protein Folding Problem and Tertiary Structure Prediction*, Merz et al., eds, Birkhauser, Boston, pp. 433-506). It is known in the art that even single amino acid changes or differences in a protein's amino acid sequence can have dramatic effects on the protein's function. For example, Wang et al (2001. J. Biol Chem. 276:49213-49220) show that a single amino acid determines the lysophospholipid specificity of the SIP1 (EDG1) and LPA1 (EDG2) phospholipd growth factor receptors (abstract); a single amino acid influences the specificity for S1P or LPA (page 49213, 2nd column, last paragraph). However, Applicant has provided little or no guidance to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Even if an active or binding site were identified in the specification, this may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity.

Thus, applicants have not provided sufficient guidance as to how to make biologically active variants of any homodimer-forming chemokine, or specifically

biologically active variants of SEQ ID NO:2, nor how to use variants which do not retain the required biological activity without undertaking undue experimentation.

Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and screen same for activity, and to determine how to treat ***any*** autoimmune, inflammatory or infectious disease with the methods of the instant invention, the lack of direction/guidance presented in the specification regarding which structural features are required to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and establishes that active MCP-1 is necessary to treat many infectious diseases, and the breadth of the claims which fail to recite any structural or functional limitations, and recite treatment or prevention of any autoimmune, inflammatory or infectious disease, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Written Description

Claims 24, 25, 28, 29-31, 34-37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph.

Claim 24, the independent claim of the instant invention recites a method of treatment comprising administration of ***any*** monomeric variant of any homodimer-forming chemokine wherein said variant results form at least one amino acid substitution that alters the pattern of hydrogen bonds at the

dimerization interface of said chemokine; claim 25 recite the additional limitation that said variant be an active mutant of the polypeptide of SEQ ID NO:2 (the elected species) a variant of CCL2 (MCP-1).

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is whatever is now claimed (see page 1117). A review of the language of the claims indicates that these claims are drawn to methods comprising administration of a genus of polypeptides, i.e., monomeric variant of any homodimer-forming chemokine wherein said variant results form at least one amino acid substitution that alters the pattern of hydrogen bonds at the dimerization interface of said chemokine. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

The specification teaches administration of several species of the claimed genus that is within the scope of the claimed genus, *i.e.* SEQ ID NO:2, which has a single amino acid substitution at position 8 in human CCL2, (Example 3), SEQ ID NO:2 with a further mutation to isoleucine at position 64 (SEQ ID NO:4) [paragraph 0012-0013], SEQ ID NO:2 or SEQ ID NO:4 missing the N-terminal glutamine residue, or comprising alanine or glycine at the N-terminus [paragraph 0150], SEQ ID NO:2 or SEQ ID NO:4 variants comprising a cysteine in position

8, 14, 17 or added on to the C-terminus (Figure 7A). However, the present claim encompasses numerous species that are not further described.

As disclosed above, the art provides some guidance as to structure-activity relationships among chemokines and teaches the importance of the amino-terminal region in binding of the chemokine to its cognate receptor. The art also teaches (See, for example, Rollins et al US 5,705,360, the '360 patent) a truncation mutation with deletions of amino acid residues 2-7 of MCP-1 (the chemokine of the elected sequence). This truncation mutation does not form dimers (column 4, lines 5-6) and acts as a potent and specific inhibitor of monocyte chemotaxis (column 4, lines 48-50).

However, in the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed genus, which is a method of treatment comprising administration of a monomeric variant of **any** homodimer-forming chemokine wherein said variant results form at least one amino acid substitution that alters the pattern of hydrogen bonds at the dimerization interface of said chemokine; One of skill in the art would not recognize from the disclosure that the applicant was in possession of the genus. The specification does not clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed (see *Vas-Cath* at page 1116).

Therefore, only methods of treatment comprising administration of monomeric variants comprising SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:2 or SEQ ID NO:4 missing the N-terminal glutamine residue, or comprising alanine or glycine at the N-terminus or SEQ ID NO:2 or SEQ ID NO:4 variants comprising a cysteine in position 8, 14, 17 or added on to the C-terminus or comprising the truncation mutation with deletions of amino acid residues 2-7 of MCP-1 (as taught by the '360 patent) or any of the above variant comprising a constant region of a human immunoglobulin heavy chain, but not the full breadth of the claims meet the written description provision of 35 U.S.C. 112, first paragraph.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 115).

35 U.S.C. § 102:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 24, 25, 36, and 37 are rejected under 35 U.S.C. 102(b) as being anticipated by Rollins et al., (US 5,705,360, the '360 patent).

The claims of the instant invention are drawn to a method of treating or preventing autoimmune, inflammatory, or infectious diseases comprising the administration of an effective amount of a monomeric variant of a homodimer-forming chemokine (Claim 24) wherein the monomeric variant may be an active mutant of SEQ ID NO:2 (the elected species) (Claim 25), wherein the disease is multiple sclerosis (the elected species), (claims 36 and 37).

The specification teaches "the term "active" means that such alternative compounds should maintain the functional features of the CCL2 (MCP-1) mutants .... i.e. should antagonize CCL2 in vivo and inhibit cell recruitment and/or inflammatory reactions [paragraph 0038]. The antagonistic properties of the monomeric variants of homodimer-forming chemokines can be maintained, or even potentiated, in the active mutants. This category of molecules includes natural or synthetic analogs of said sequence, wherein one or more amino acid residues have been added, **deleted**, or substituted, provided they display the same biological activity [paragraph 0041, emphasis added by the Examiner]. The specification teaches that SEQ ID NO:2 is a variant of wildtype CCL2 (MCP-1).

The '360 patent teaches a method of treatment comprising administration of a mutant chemokine to a patient for treatment of a chemokine mediated disease such as inflammation or an autoimmune disease (column 6, lines 55-59). Administration of inhibitors to the recruitment of leukocytes would be useful in treating autoimmune diseases, such as rheumatoid arthritis, inflammatory bowel disease and **multiple sclerosis**, chronic pulmonary inflammation, such as pulmonary fibrosis, and other conditions linked to the recruitment of leukocytes, such as monocytes (column 6, line 59, bridging column 7, line 2, emphasis added by Examiner). The reference teaches administration of an MCP-1 (CCL-2) derivative (column 7, lines 29-30). The mutated MCP-1 derivative may be the 7ND derivative. This derivative corresponds to the MCP-1 peptide with deletions of amino acids 2 to 7 at the N-terminus (column 3, lines 31-33); this N-terminal deletion mutant does not form dimers (column 4, lines 5-6). The mutant chemokine can additionally contain other mutations as well. For example, one or more amino acids of the chemokine can additionally be deleted, substituted or added. The additional mutation can, for example, enhance the inhibitory activity of the mutant cytokine (column 3, lines 34-38). It is the Examiner's position that the variants of MCP-1 taught by the '360 patent meet the limitations of the variants described in Claims 24, and 25, given the claims broadest, reasonable interpretation in light of the above teachings of the specification of the instant invention in that the reference teaches mutations comprising variants of MCP-1 comprising substitutions or deletions such that the variants are unable to form dimers and have the required biological activity of treating inflammatory or autoimmune diseases.

Thus, the teachings of the '360 patent anticipate the limitations of claims 24, 25, 36, and 37.

35 U.S.C. § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 30, and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over the '360 patent as applied to claims 24 and 25, in view of Herrmann et al (US 6,100,387, the '387 patent).

The teachings of the '360 patent are outlined in detail above. In addition to the teachings above, the '360 patent teaches fusion proteins comprising an MCP-1 mutation and the FLAG epitope (column 8, lines 62-62, Figure 1B). The '360 patent does not teach a method comprising administration of a chemokine variant wherein the monomeric variant comprises a constant region of a human immunoglobulin heavy chain. The '387 patent teaches chimeric polypeptides containing chemokine polypeptide domains. The chemokine polypeptides comprise chemokine domains covalently attached to heterologous polypeptides (column 1, lines 6-10). "Heterologous polypeptides" include all polypeptides that can be covalently attached to a chemokine polypeptide, including without

limitation immunoglobulins, and antibody-binding tags such as His, Flag, or myc. For example, chemokine polypeptides can be attached to the Fc portion of an immunoglobulin (column 8, lines 52-63). The skilled artisan is aware that the Fc fragment comprises parts of the heavy chain constant regions of the immunoglobulin molecule.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to generate monomeric variants of the chemokine of the instant invention comprising a constant region of the human immunoglobulin heavy chain, as taught by the '387 patent in place of the chemokine variant-FLAG fusion protein taught by the '360 patent and utilize said fusion proteins in the treatment methods taught by the '360 patent. The person of ordinary skill in the art would have been motivated to make these modifications and would have a reasonable expectation of success because the '387 patent teaches chimeric polypeptides containing chemokine polypeptide domains and immunoglobulins, or antibody-binding tags such as FLAG. Additionally, one of ordinary skill in the art would be motivated to make such a modification because the art teaches that Fc fusion proteins have increased serum half-lives (See, for evidentiary purposes only, Gillies et al. US 6,617,135, column 3, lines 5-7).

Claims 26, 28, 29, 34, 35 and 44 are free of the prior art.

Art made of record:

The following art is made of record and not relied upon is considered pertinent to applicant's disclosure. Toran Garcia et al. (2007. WO 2007/113285) disclose a chemokine fusion protein comprising Human CCL2 (P8A) mature protein, which is 100% identical to SEQ ID NO:2 of the instant invention (See results in SCORE and alignment below. The protein can be used to treat inflammatory or autoimmune diseases in which chemokine receptors are involved (abstract).

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  Query Match             100.0%;  Score 402;  DB 1;  Length 76;
  Best Local Similarity   100.0%;  Pred. No. 4.3e-42;
  Matches   76;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 QPDAINAAVTCCYNFTNRKISVQRLASYRRITSSKCPKEAVIFKTIVAKEICADPKQKWV 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 QPDAINAAVTCCYNFTNRKISVQRLASYRRITSSKCPKEAVIFKTIVAKEICADPKQKWV 60

Qy         61 QDSMDHLDKQTQTPKT 76
              ||||||||||||||||
Db         61 QDSMDHLDKQTQTPKT 76
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However, the reference is not available as prior art, since the filing date of the reference is after the earliest priority date of the instant invention.

Conclusion:

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHULAMITH H. SHAFER whose telephone number is (571)272-3332. The examiner can normally be reached on Monday through Friday, 8 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao, Ph.D. can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Shulamith H. Shafer/
Examiner, Art Unit 1647